REMARKS

Claims 1-65 are now pending, with claims 51-53 withdrawn. Applicants are herein amending claim 1.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-50 and 54-65 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Applicants have amended claim 1 relating to "such as," which is believed to render the rejection moot with regard to claims 1-50, 63, and 65. Applicants traverse the remaining rejections to claims 54-62, and 64.

Claims must be examined as a whole. *See* MPEP 2173.02. When read as a whole, it becomes clear that "surgery" and "anesthesia" are preceded by "neuronal loss associated with." Thus, the claim is both clear and definite.

As to "an adverse consequence of overstimulation of one or more excitatory amino acids," Applicants submit that 1) the consequences, 2) the amino acids, and 3) their relationship, are well known to those of skill in the art, and thus, the scope of the claim is clear to a person possessing the ordinary level of skill in the art.

Accordingly, Applicants respectfully request withdrawal of the rejection of claims under 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 41, 42, 44, 45, 54, 55, 60, 61, 63, and 64 are rejected under 35 U.S.C. §112, first paragraph as allegedly not enabled for methods of treating conditions including tumor growth, metastasis, restenosis, inflammation, neuronal loss associated with stroke, neurodegenerative disease, adverse consequence of overstimulation of one or more excitatory amino acids, Alzheimer's disease, and Parkinson's disease.

When rejecting a claim for lack of enablement, the "examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure." MPEP §2164.04 citing *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Applicants believe that a prima facie case has not been

established, as required by MPEP §2164.04. As the enablement rejection is improper, Applicants respectfully request that the rejection be withdrawn.

Applicants' disclosure contains sufficient information for one skilled in the art to make and use the claimed invention. The examples and descriptions provide more than an adequate amount of direction for one skilled in the art, which precludes a finding that undue experimentation would be required. Applicants respectfully request reconsideration of this rejection, because the evidence of record does not demonstrate that those skilled in the art would be unable to practice the claimed inventions. As stated in MPEP §2164.01:

> There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:
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> (A) The breadth of the claims;
> (B) The nature of the invention;
> (C) The state of the prior art;
> (D) The level of one of ordinary skill;
> (E) The level of predictability in the art;
> (F) The amount of direction provided by the inventor;
> (G) The existence of working examples; and
> (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
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> *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

When rejecting a claim under the enablement requirement of §112, the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why [he/she] believes that the scope of protection provided by [the] claim is not adequately enabled by the description of the invention provided in the specification." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the Examiner must provide evidence or technical reasoning substantiating those doubts. *Id.* and MPEP §2164.04. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 27 U.S.P.Q.2d at 1513.

Significantly, the Office Action fails to provide facts indicating that Applicants' disclosure would not enable those skilled in the art to practice the claimed inventions. Although the Office Action discusses certain factors to be considered in relation to this issue,

a review of this discussion reveals that the factors do not, in fact, support rejection of the instant claims.

The Office Action's main contention appears to be that the invention just wouldn't work. This is not the test for enablement. Applicants have developed novel and nonobvious integrin antagonists (as evidenced by the fact that no prior art is cited against the claims), and have claimed methods for treating disorders in which such antagonism would be expected to have a therapeutic effect. There is no requirement that Applicants engage in clinical testing before filing their application. *In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (because pharmaceutical inventions usually require further research and development, incentive to fully research and develop vital drugs and potential cures would be completely removed were such inventions not patentable long before being optimized or ready for human use). Applicants have shown the basic pharmacological activity as antagonists (*see, inter alia, Applicants' specification* at page 197, Table 1), and that should be sufficient.

Breadth of the Claims

The Office Action appears to consider the claims overly broad based on the assessment of the state of the prior art discussed below. However, Applicants note that the Office Action unnecessarily focuses on the disparate causes for disorders rather than the recognizable common pathways or symptoms. For example, "tumor growth" is not as broad as the Office action would imply. Certainly, there may be numerous **causes** of tumors, but as noted in the Office Action, **all tumors, whether benign or malignant, are characterized by cellular proliferation**, and thus the claims to both benign and malignant tumors are not overly broad.

Nature Of The Invention

The Office Action simply characterizes the nature of Applicants' inventions, but does not allege, much less demonstrate, that the nature of the invention supports a rejection for alleged lack of enablement.

State Of The Prior Art / Level Of One Of Ordinary Skill

Tumor Growth and Metastasis: The Office action alleges that treatment of "cancer growth" is of a relatively low skill level, mainly due to different types of cancers. Although Applicants are not bound to supply a theory of operation, they note generally that the state of the art is not as bleak as the Office Action implies. Certainly, as noted above, there may be numerous causes of tumors, but as noted in the Office Action, all tumors, whether benign or malignant, are characterized by cellular proliferation. As stated in a recent review by Kumar (*Current Drug Targets*, 2003, **4**, 123-131), tumor cells elicited a robust angiogenic response due to an increase secretion of angiogenic factors and a decrease in angiogenic inhibitors. He states "αvβ3 receptor has a central role in the process of angiogenesis downstream from all recognized angiogenic factors, suggesting that targeting this receptor any elicit significant inhibition of angiogenesis and tumor growth." *Id.* at 125. In addition, integrins play a direct, albeit less well-defined, role in tumor and endothelial cell interactions which may involve tumor invasion and establishment of metastases. Examples of supportive data include the upregulation of αvβ3 expression in the metastatic phenotype of breast cancer (G. Gasparini et al., *Clin. Cancer Res.* 2000, **6**, 2625-2634) and in prostate cells that metastasize to bone and attaché to bone through osteopontin a ligand for αvβ3 and a key component of the bone matrix (M. Edlund et al., *Cell Growth Differ.* 2001, **12**, 99-107). The evidence would suggest a role for the use of integrin antagonists in the treatment of tumor metastases.

Restenosis: The Office action does not discuss the state of the prior art or the level of skill, and offers no evidence other than an unsupported assertion that "[t]here is no such thing as being able to treat such widely diverse problems which arise from different sources." Applicants respectfully submit that this does not rise to the required level of "evidence or technical reasoning."

Inflammation: The Office action does not directly discuss the state of the prior art or the level of skill, other to allege that treating inflammation generally is "contrary to medical science." Applicants submit that the well known **symptoms** of inflammation are universal, and independent of their cause. Furthermore, the Office Action's assertion that "these types of inflammations are treated with antibiotics" is not accurate. The **cause of the inflammation** (i.e., infection) is treated with antibiotics, not the inflammation itself.

Stroke: The Office Action states, "the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation." The Examiner is reminded that "time and difficulty of experiments are not determinative if they are merely routine." MPEP §2164.06. Likewise, "the fact that experimentation may be complex does not necessarily make it undue." MPEP §2164.01. Applicant has provided more than ample direction to those skilled in the art to make and use the invention.

Neurodegenerative Disorders: Although the Office Action alleges that there are numerous types and causes of disorders, the Office Action fails to explain how such a situation would demonstrate that such persons would not be able to treat neurodegenerative diseases after reading Applicants' disclosure. There is, for example, no evidence of record demonstrating that those skilled in the art made any attempt to do so, much less failed in such an attempt. Thus, the "state of the prior" fails to demonstrate any lack of enablement.

Overstimulation of One or More Excitatory Amino Acids: Applicants note that the Office Action initially stated that "overstimulation of amino acid/amino acids is not enabled." Applicants' claim relates to "**excitatory** amino acids." The Office Action further conjectures that there might be other unknown excitatory amino acids, and that regarding adverse consequences, "enablement for such a scope is not possible since so little or nothing is known about what these consequences are." The problem of future discovery of unknown excitatory amino acids is moot. MPEP §2164.01(a) clearly states that "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, **at the time the application was filed**, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation" (emphasis added).

Alzheimer's disease: The Office Action states that "[t]he skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase." The Office Action fails to explain how such a situation would demonstrate that such persons would not be able to treat Alzheimer's disease after reading Applicants' disclosure. Thus, the "state of the prior" fails to demonstrate any lack of enablement.

Parkinson's disease: The Office Action states that "[t]he skill level in the art is such [sic] low that the only treatments available to this day are drugs that are helpful in regulating Dopamine." The Office Action fails to explain how such a situation would demonstrate that

such persons would not be able to treat Parkinson's disease after reading Applicants' disclosure. Thus, the "state of the prior" fails to demonstrate any lack of enablement.

Predictability Of The Art

The Office Action fails to explain the nature of any implied unpredictability. For example, if the only area of unpredictability relating to the claimed inventions is how much of the recited compounds one would have to administer to achieve the desired effect, such a situation would fall far short of demonstrating any lack of enablement. Since there is no evidence of record on this point, the "predictability the art factor" does not support rejection of the instant claims.

The Amount Of Guidance Presented/The Presence Or Absence Of Working Examples

The Office Action fails to provide any evidence demonstrating that those skilled in the art having the provided level of disclosure before them would not be able to practice the claimed inventions. Given Applicants' disclosure, there is no reason to believe that those skilled in the art would need to engage in anything more than routine experimentation to practice the claimed inventions. To the extent that the Office Action requires a particular number of working examples reciting specific dosages, it is well-established that an applicant need not include any working examples demonstrating a claimed invention. *In re Fouche*, 169 U.S.P.Q. 429, 434 (C.C.P.A. 1971). Thus, there is no reason to believe that more guidance, in the form of working examples or otherwise, would be needed to practice the claimed inventions. Since the Office Action did not specifically address these Wands factors, they should be deemed to support enablement of the claimed inventions.

Quantity Of Experimentation

The Office Action fails to allege that practice of the claimed inventions would entail undue experimentation on any disorder except stroke. Accordingly, there is no reason to believe that the "quantity of experimentation" involved would be so great that those skilled in the art would not be able to practice the claimed inventions.

Thus, as is evident from the foregoing analysis, the Office Action's unsupported contentions as to alleged difficulties that those skilled in the art would encounter in practicing the claimed inventions simply do not constitute evidence or technical reasoning of the sort required to substantiate allegations that there is a lack of enablement. Absent such a showing, there is no reason to believe that those skilled in the art, reading Applicants' disclosure, would not have been able to make and use the recited compounds.

Accordingly, the rejection under §112, first paragraph, is improper and should be withdrawn.

The Examiner is cordially invited to call the undersigned if the Examiner has questions or concerns.

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